

Hyperbilirubinemia in Inflammatory Pancreatic Disease:

Natural History and Management

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Of 868 patients admitted with pancreatitis between 1971 and 1976, coexisting hyperbilirubinemia was noted in 125 (14%). The patient population was primarily composed of alcoholics (84%) with chronic pancreatic disease (75% Marsielles Class II or higher) which was of moderate severity (77% fewer than three prognostic signs). The hyperbilirubinemia in these 125 patients was due to extrahepatic obstruction in 22%, hepatocellular disease in 31%, and was idiopathic in 47%. Transient hyperbilirubinemia (< 10 days duration) occurred most commonly in the idiopathic group. Transitory periductular pancreatic edema may account for the elevated bilirubin in some of these cases. Liver biopsy should be done whenever hyperbilirubinemia persists longer than ten days in patients with pancreatitis. If hepatocellular disease is not found, transhepatic or endoscopic retrograde cholangiography are indicated. If common bile duct obstruction is demonstrated, a brief trial of medical therapy is in order. Persistent conservative treatment, however, exposes the patient to the risk of cholangitis and biliary cirrhosis. In 13 of the 125 cases (10%), persistent extrahepatic obstruction proved to be due to compression of the common bile duct by inflammatory pancreatic tissue. In these circumstances, choledochoduodenostomy is recommended as the procedure of choice. In patients requiring biliary decompression, concomitant procedures upon the pancreas are occasionally indicated.

FOR MORE THAN 80 YEARS it has been known that obstructive jaundice may result from inflammatory pancreatic disease.¹⁰ Although a number of studies have appeared in the recent literature^{4,7,11,12} fewer than 100 documented cases of jaundice due to benign pancreatic disease have been reported. Since each of the previous communications has been restricted to describing a small number of surgical cases, the general approach to the management of patients with hyperbilirubinemia and pancreatitis continues to be problematic.

How frequently do pancreatitis and hyperbilirubinemia coexist? When does the demonstration of an elevated bilirubin in patients with pancreatitis indicate

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the necessity for surgery? What are the risks in untreated cases? What is the preferred surgical technique?

The purposes of the present study are twofold: 1) to provide both incidence and natural history information in order to more clearly define therapeutic roles in this condition and, 2) to describe our experiences in the management of thirteen cases requiring surgical correction.

Patient Data

Records of all patients with a diagnosis of pancreatitis admitted to Grady Memorial Hospital between 1971 and 1976 were reviewed. In 868 patients, the clinical diagnosis of pancreatitis was substantiated by characteristic upper abdominal pain and constitutional symptoms, abdominal tenderness, and elevated serum and/or urine amylase. Patients not meeting these criteria or those subsequently proved not to have pancreatitis were excluded. In recent years, the diagnosis of pancreatitis has frequently been confirmed by demonstrating an elevated amylase clearance.

Of the 868 patients with pancreatitis, 125 (14%) also exhibited a total serum bilirubin greater than 1.5 mg/100 ml. It is with these 125 patients with pancreatitis and hyperbilirubinemia that the present study is concerned.

The *type* of pancreatitis present in these 125 patients is considered in Table 1. That this study is weighted toward a more chronic form of pancreatitis is evidenced by noting that three patients out of four were Marsielles Class II or higher. Chronic alcoholism was predominant in 105 (84%) of these 125 patients. Cholelithiasis was the primary feature in 11 (9%), and in five cases (4%), both alcoholism and cholelithiasis were present.

The *degree* or severity of the pancreatitis exhibited by these patients is shown in Tables 2 and 3. Ninety-six patients (78%) exhibited fewer than three of those signs

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TABLE 1. *Type of Pancreatitis in the Study Group**

Class	Type	
I	Acute	27
II	Acute relapsing	51
III	Chronic relapsing	39
IV	Chronic	2
		125

* Marsielles classification.

known to be of prognostic significance.⁹ Of note is that the mortality rate was seven times higher when three or more of the prognostic signs were present. In addition to the nine in-hospital deaths, an additional 16 patients subsequently expired from various causes making the total known mortality rate 25/125 (20%). As an additional reflection on the severity of the underlying pancreatitis in these patients, 44 of these 125 patients (35%) required at least one readmission during the study period for recurrent pancreatitis.

Significant features of the past medical history included a history of upper gastrointestinal bleeding in 41, alcoholic ketoacidosis in 22, profound weight loss in 22, and insulin dependent diabetes mellitus in eight cases.

The physical findings in this group of patients primarily reflected the acute nature of the episode; abdominal tenderness was noted in 114, and body temperature was elevated above 38.5° in 72 patients. Liver percussion exceeded 12 cm in 33 cases.

Three laboratory values were of specific interest (Table 4). Although total bilirubin was abnormally elevated in *each* of the 125 patients, the highest value recorded was less than 6 mg% in 108 cases (86%). Amylase was elevated in 98 of the 115 cases in which it was measured.

The causes of the hyperbilirubinemia in the 125 patients with coexisting pancreatitis are listed in Table 5. Fifty-eight patients exhibited a mild elevation of bilirubin returning to normal within ten days. Work-up of these patients was not extensive and they are accordingly classified as idiopathic. Sixteen patients were found to have biliary lithiasis. In none of these patients,

TABLE 3. *Severity of the Associated Pancreatitis*

Number of Prognostic Signs	Number of Patients	Hospital Deaths	Mortality Rate
0	28	0	3/96 (3%)
1	39	2	
2	28	1	
3	13	3	6/29 (21%)
4	10	0	
5	1	1	
6	5	2	
7 or >	—	—	
	125	9	9/125 (7%)

however, including six with choledocholithiasis, could any stricture of the common bile duct be demonstrated at surgery. Of interest is the observation that only 28 of these 125 patients (22%) harbored surgically correctable hyperbilirubinemia.

Of the 125 patients with pancreatitis and hyperbilirubinemia, only 13 (10%) underwent operative correction for compression of the common bile duct by pancreatic tissue (Table 6). That inflammatory pancreatic disease uncommonly results in significant common bile duct obstruction is further emphasized by the observation that of the 868 patients in this study admitted for pancreatitis, only 1.4% required surgery for hyperbilirubinemia due solely to pancreatitis.

Sufficient clinical suspicion of common bile duct obstruction to warrant investigation of bile duct morphology arose whenever *persistent* hyperbilirubinemia was demonstrated. In 58 of 92 cases in whom it was possible to determine the duration of hyperbilirubinemia, serum bilirubin returned to normal within 10 days or less. All 13 of the patients eventually shown to have common bile duct obstruction requiring surgery were in the group of 34 patients with hyperbilirubinemia persisting longer than ten days. Patients requiring surgery also exhibited significantly higher average values for total bilirubin 12.6 ± 1.9 mg% and for alkaline phosphatase 986 ± 160 mu ($p < .01$).

Discussion

Since the terminal portion of the common bile duct is encased by pancreatic tissue in 60–80% of patients,⁵

TABLE 2. *Prognostic Signs**

Admission		First 48 Hours	
Prognostic Sign	No. Patients	Prognostic Sign	No. Patients
LDH > 350 IU	52	CA < 8 mg%	26
Glucose > 200 mg%	35	Hct decrease > 10 units	11
SGOT > 250 sfu	26	Pao ₂ < 60 torr.	9
Age > 55 years	17	BUN increase > 5 mg%	8
WBC > 16,000 mm ³	15	Base deficit > 4 meg/L	7
		Fluid sequestration > 6 L	6

* After Ranson, et al.⁹TABLE 4. *Serum Values of Interest*

	Normal	Avg. + SEM	Range
Amylase	<200 Somogyi U.	687 ± 119	39–5400
Total bilirubin	<1 mg%	3.9 ± 0.4	1.5–28
Alkaline phosphatase*	5–13 King-Armstrong U. 35–100 milliunits	30.9 ± 5.5 196.0 ± 17.0	7.9–124 38–900

* Reported in KA during 1971–72; milliunits in 1973–1976.

TABLE 5. *Causes of Hyperbilirubinemia in 125 Patients with Pancreatitis*

Medical causes		
Alcoholic hepatitis	19	
Cirrhosis	8	
Drug induced	6	
Hepatitis (+ Australia Ag)	4	
Hemolysis	2	
	39	(31%)
Obstruction of bile duct		
Benign pancreatic disease	13	
Cholecystolithiasis	10	
Choledocholithiasis	6	
	29	(22%)
Idiopathic	58	(47%)
	125	(100%)

it is not surprising the hyperbilirubinemia occurs in patients with benign pancreatic disease. Rather, it seems remarkable that jaundice does *not* accompany pancreatitis even more frequently.

Initial recognition that chronic pancreatitis could cause compression of the common duct has been credited to Riedel¹⁰ who reported a single case in 1896, although Mayo-Robson reported a series of 10 cases in 1904, one of which had been operated upon in 1892.⁶ Since that time, a number of smaller anecdotal reports have appeared concerning this condition.^{2,3,7,8,11-13} Presently, however, there are fewer than 100 documented cases in the literature.

Despite the infrequent reporting of such cases, it is likely the hyperbilirubinemia secondary to pancreatitis is more common than generally appreciated. Frieden examined 300 autopsy records of patients with acute pancreatitis and found 25% with coexisting jaundice. Only 16%, however, were due to pancreatic encroachment on the common duct.³ By being limited to autopsy material and correspondingly severe disease, these incidence data may not reflect the entire disease spectrum of pancreatitis. Weinstein and his coworkers similarly estimated the incidence of jaundice in pancreatitis to be 15-25%.¹³ They further proposed that periductal pancreatic edema could account for the *transient* obstructive jaundice observed in some patients with acute pancreatitis.

In the present study, we found that while hyperbilirubinemia occurred in 125 of 868 patients with pancreatitis (14%), hyperbilirubinemia could be solely attributed to pancreatitis or its complications in only 10%. (13/125). What proportion of the 58 "idiopathic" patients with transient hyperbilirubinemia were in fact due to pancreatic causes was not determined in this study. It is likely that hyperbilirubinemia in some of these patients was due to compression of the intrapancreatic portion of the common duct by edema arising from the adjacent pancreatitis.

Accordingly, these data suggest that a rational plan of management for hyperbilirubinemia coexistent with pancreatitis would consist of initial supportive treatment and observation. Should hyperbilirubinemia persist longer than ten days, liver biopsy should be considered. In approximately 25% of our cases, the liver biopsy was diagnostic of primary hepatocellular disease. If the liver biopsy shows cholestasis, visualization of the biliary duct system by endoscopy or thin needle cholangiography would seem indicated. Radiographic demonstration of a dilated common bile duct taken in conjunction with an elevated alkaline phosphatase and hyperbilirubinemia is definitive proof of significant obstruction.

A brief trial of conservative therapy is probably warranted in patients with persisting obstruction. However, if both the elevated alkaline phosphatase and total bilirubin do not promptly return to normal, continued medical treatment may expose the patient to the risk of cholangitis. Cholangitis occurred in two of the thirteen patients undergoing surgery in this study (cases 2 and 11), and has been reported by others.^{4,12} Furthermore, long standing obstruction even of a relatively mild degree, apparently disposes toward biliary cirrhosis.¹² In this regard, an isolated persistent elevation of alkaline phosphatase may be the earliest expression of significant duct obstruction, and, when found, should initiate investigation.

Surgical treatment is quite successful in relieving persistent biliary obstruction. Although a variety of techniques for biliary drainage can be used, choledochoduodenostomy and Roux-en-y cholecystojejunostomy have provided the best long term results.^{11,12} In our opinion, choledochoduodenostomy offers three advantages over Roux-en-y cholecystojejunostomy or Roux-en-y choledochojejunostomy: 1) bile is not diverted from the duodenum 2) future pancreatic surgery is not compromised, and 3) stricture of this anastomosis is decidedly uncommon. We believe that whenever choledochoduodenostomy is done, cholecystectomy should be added in order to prevent accumulation of food debris refluxed into the common duct.

Regardless of which technique is chosen, it is imperative to construct a large biliary-intestinal stoma in order to prevent postoperative stricture and subsequent episodes of cholangitis.

In addition to biliary drainage, concomitant procedures upon the pancreas may occasionally be indicated. In particular, pseudocysts should be drained at the same time that biliary obstruction is relieved. If the pseudocyst is in the head, cystoduodenostomy may be chosen. It is important to obtain an operative cholangiogram after drainage of pseudocysts in the head of the pancreas, since biliary obstruction may be due to causes other than the pseudocyst itself (cases

TABLE 6. *Patients Requiring Surgical Relief of Common Bile Duct Obstruction Caused by Inflammatory Pancreatic Disease*

	Age	Sex	Duration of Hyperbilirubinemia	Findings at Surgery	Operation	Results
1	49	M	2 Months	Mass in head of pancreas	Roux-y cholecystojejunostomy Biopsy—chronic pancreatitis	Occasional episodes of pancreatitis in 2 yr. follow-up
2	39	F	3 Weeks	Inflammatory mass in head Suppurative cholangitis	Exploration and T-Tube Drainage of common duct	No recurrence in 18 months
3	49	F	2 Weeks	Pseudocyst in head of pancreas	Cystoduodenostomy	Expired 14 days later in renal failure. Autopsy showed obstruction of common duct by chronic pancreatitis
4	42	M	9 Weeks	Firm mass in head of pancreas	Roux-y cholecystojejunostomy	Occasional episodes of pancreatitis in 3 yr. follow-up
5	39	M	2 Weeks	Pseudocyst in head of pancreas	Cystoduodenostomy Biopsy—chronic pancreatitis	Asymptomatic 1 yr. follow-up
6	54	M	2 Weeks	Pseudocyst in head Ampullary stenosis	Cystoduodenostomy Sphincteroplasty Biopsy—chronic pancreatitis	Recent discharge
7	49	F	4 Months	Firm mass in head of pancreas	Roux-y cholecystojejunostomy	Expired 5 yrs. later in alcoholic ketoacidosis. Autopsy showed fibrotic obstruction of common duct.
8	42	M	4 Weeks	Firm mass in head of pancreas	Choledochoduodenostomy Biopsy—chronic pancreatitis Incidental cholecystectomy	Recent discharge
9	36	M	5 Weeks	Firm mass in head of pancreas	Choledochoduodenostomy	Asymptomatic for 6 months
10	47	F	6 Weeks	Large mass in head of pancreas	Cholecystojejunostomy with enteroenterostomy	No recurrence in 5 yrs.
11	32	F	2 Months	Mass in head of pancreas Ascending cholangitis	Roux-y choledochojejunostomy Cholecystectomy	Asymptomatic for 1 yr.
12	31	F	6 Weeks	Mass in head of pancreas	Choledochoduodenostomy Biopsy—chronic pancreatitis Incidental cholecystectomy	Occasional episode of pancreatitis during 3 yr. follow-up
13	41	M	3 Weeks	Large mass in head of pancreas Duodenal obstruction	Whipple procedure Biopsy—chronic pancreatitis	Asymptomatic for 6 months

3 and 6). One of our patients (case 13) underwent pancreaticoduodenectomy when persistent obstructions of the common bile duct, the pancreatic duct, and the duodenum were demonstrated. It should be kept in mind that biliary drainage alone does not offer any respite from the ongoing fibrotic process in the pancreas, and that continued symptoms may require corrective pancreatic surgery at some future time.

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